Blistering Diseases

Introduction

This lesson is going to be about the blistering diseases of the skin. Blisters are called vesicles when they are small (< 1 cm) and bullae when they are large (> 1 cm). Lots of things can cause blistering, including burns or just wearing a new pair of heels without socks. The diseases in this lesson are severe blistering diseases, caused by autoimmunity or infection, and are not the routine blistering of skin commonly seen.

We start with a review from Skin #1: *Introduction to Skin*, then dive into the blistering diseases. The stratum basale, comprising the stem cells of the epithelium, is anchored down to the basement membrane by hemidesmosomes. Those stem cells are attached to the cells above them by desmosomes. Every cell in the epithelium, basale to corneum, is attached to its neighbor by desmosomes. Desmosomes link cells together using extracellular proteins such as desmoglein, and anchor to the inside of a cell using a plaque named desmoplakin. The epidermis is above the dermis. The epidermis and dermis are separated by the basement membrane. The basement membrane is not a flat, horizontal line, but rather it has peaks and valleys. The peaks of the dermis into the epidermis are called papillae. The valleys of epidermis dipping into dermis are called rete ridges.

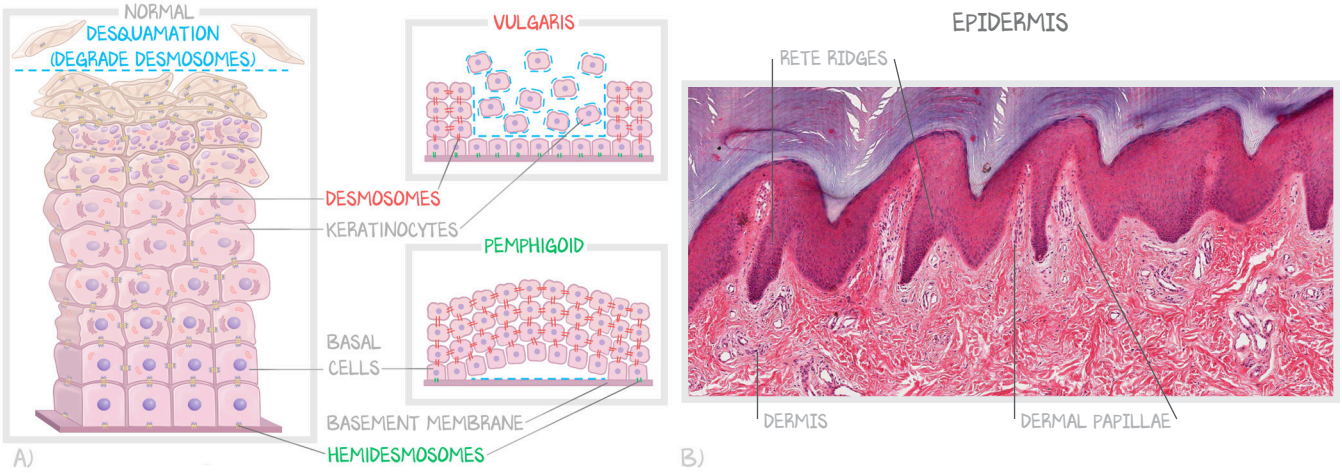


Figure 3.1: Visualizing the Epidermis
(a) An illustration of the epidermis shows the two main connections found in the epidermis. The basal cells are anchored to the basement membrane by hemidesmosomes. The basal cells are connected to the most recent keratinocyte daughter by desmosomes, and every keratinocyte to corneocyte that is part of the epidermis is connected to its neighbors by desmosomes. (b) Histology slide identifying the Rete ridges and Dermal Papillae of healthy skin. Knowledge of both the connections of keratinocytes and the structural vocabulary is essential for mastering the content in this lesson.

You are going to notice significant overlap between several diseases. Mucosal involvement, target lesions, blisters. Intra-epidermal lysis, dermal-epidermal junction. Don't focus on the overlap. Don't rely on buzzword recognition to get you through this content. It is actually quite easy to master blistering disease, because each disease is self-contained and is not meant to be compared or contrasted with another. Here, even more than in most lessons, we emphasize mastering the pathogenesis to presentation and pathogenesis to biopsy results for these diseases.

We cover pemphigus vulgaris and bullous pemphigoid first, then teach dermatitis herpetiformis as the "other one with immunofluorescence." These three diseases are mediated by antibodies. We close with the drug reactions of erythema multiforme and of the SJS/TEN spectrum. These two diseases are not antibody-mediated, and are considered both cell-mediated immune response and drug reactions.

Pemphigus and Pemphigoid—You're Naming Them Wrong

The similarities in the names of the diseases, the immunoglobulin, and even the names of the targets make these two diseases—bullous pemphigoid and pemphigus vulgaris—difficult for students. They are clearly different diseases, so from this point forward we will call them Vulgaris and Pemphigoid. Naming one Vulgaris and the other Pemphigoid (as opposed to using their real names, as in the title of this section) helps separate them mentally—there is no similarity in these nicknames. Learning the pathogenesis as, "Vulgaris is the loss of squamous cells from each other" and "Pemphigoid is loss of basal cells from the basement membrane," rather than by the immunoglobulin target, also helps eliminate ambiguity. After all, desmosomes, hemidesmosomes . . . which is the BM one again? When you master this lesson, reading this paragraph is insulting. When you first start learning the lesson? You're welcome. Don't learn this table. Don't compare them when you study. This table is designed to show you how OPPOSITE they are; the only way you can get fooled is by the words that name them.

Unless you become a dermatologist there is ONE Pemphigus (Vulgaris) and ONE Pemphigoid.

	VULGARIS	PEMPHIGOID
Ig	IgG	IgG
Target	Squamous cell connections Desmosomes	Basal cells to basement membrane Hemidesmosomes
Blisters	Thin, tear easily, + Nikolsky	Thick, don't tear, fluid filled, – Nikolsky
Location	Anywhere, including mouth	Only on keratinized skin
Immuno	IgG and C3 around every cell Reticular pattern	IgG only at the basement membrane Linear pattern
Light	Separation from BM and from each other Acantholysis	Separation from the BM but attached to each other

Table 3.1: Pemphigus Vulgaris vs. Bullous Pemphigoid
Because they share words—desmosome, IgG, Nikolsky, "pemphig-" in their names—students confuse these diseases. But they are nearly opposites. Don't memorize this table. Learn the diseases as distinct illness scripts, and you won't have trouble.

Pemphigus Vulgaris = *"Vulgaris"*

Pemphigus **Vulgaris** is the bad one, it is more vulgar than its close cousin, Pemphigoid. Vulgaris is an autoimmune disease caused by **IgG antibodies against desmosomes**, usually targeting **desmoglein**, the extracellular cadherin molecules of desmosomes. This causes destruction of the desmosomes, and so is considered a cytotoxic antibody-mediated hypersensitivity reaction (**type II HSR**). This causes every cytoplasmic bridge, every connection one keratinocyte has with all of its neighbors, to be destroyed. Every connection between every cell of the skin layer is lost. The process by which the most apical layer of keratinized cells leaves the epidermis is a process called **desquamation** and is controlled by proteolytic cleavage of the desmosomes. With Vulgaris, the entire epidermis desquamates at once. The **hemidesmosomes are spared**, so the stem cells of the stratum basale remain intact with the basement membrane below.

Every squamous cell falls off from every other squamous cell and also off from the basal cells. Since none of the cells is attached to any another, the **blisters** this disease presents with are going to be **flaccid intraepidermal bullae** (paper-thin and flimsy) that are easily torn, called a **positive Nikolsky sign**. The blister forms because the cell layer is not connected to the basement membrane. The blister tears easily because the cells are not attached to one another. Vulgaris, being the more vulgar one, **does present with oral lesions**. This condition can be fatal, and should be treated just like a full-thickness burn. Without the epidermis, fluid and temperature regulation are lost. Without the keratinized layer to prevent debris, the dermis is exposed, and more easily infected or inoculated with foreign particles.

If the patient survives, there **can be** complete healing of these lesions **without a scar**. This is because the basal layer is intact. If the antibodies go away, the basal layer will just keep doing what it always does, and make more squamous cells, replacing the skin as if the blister never happened. There is no need for the epidermal layer to migrate, no stimulus to incite fibroblasts to lay down collagen. The basement membrane wasn't compromised, so the skin can just fix itself . . . as long as there aren't any antibodies around.

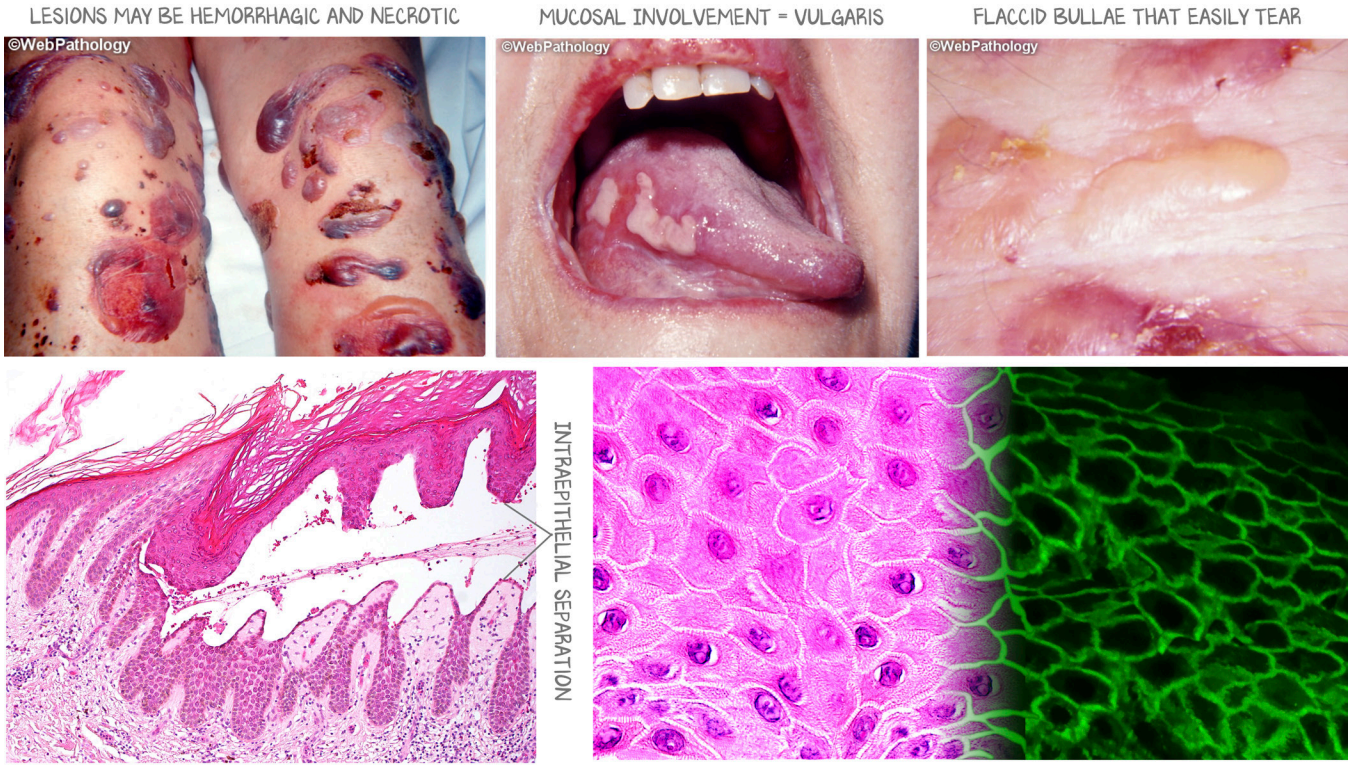


Figure 3.2: '*Vulgaris*' (Pemphigus Vulgaris)
Pemphigus vulgaris results in flimsy blisters that rupture easily, often involves the mucocutaneous and mucous membranes as well as skin, and can occur anywhere. Pemphigus vulgaris is caused by antibodies that target desmosomes—intercellular bridges—resulting in the detachment of keratinocytes from one another (intraepithelial separation). However, because hemidesmosomes (which aren't targeted) attach the basal cells to the basement membrane, there is a suprabasal (basal cells hang on to the basement membrane) intraepidermal (the cells separate from each other) blister. On immunofluorescence, the antibodies colocalize with desmosomes, resulting in a fish-net pattern encircling the keratinocytes (intercellular deposition of IgG and complement C3).

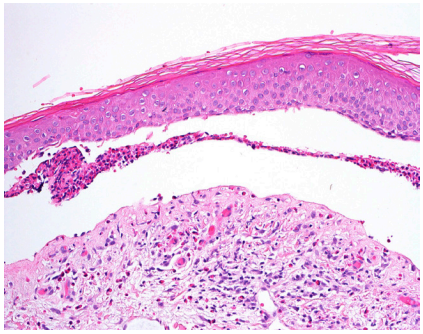
A confirmation of the diagnosis is made on biopsy. That biopsy can be delivered to you in two ways: immunofluorescence or light microscopy. On **immunofluorescence**, there will be **deposition of IgG and C3** around the epidermal cells. There will be deposition around each and every epidermal cell. This will outline every cell in the epidermis—the plasma membrane lights up but the cell itself does

not, creating a **reticular pattern** (the slide looks like a green net). That green net is separated from the dermis. On **light microscopy**, on high magnification, you will see **tombstoning** on the basement membrane—periodic stem cells found still attached to the BM. This is also known as **retention of the basal keratinocytes**. On a lower magnification you will be able to see the blister, separated from the BM by free space, with **acantholysis** (separation of keratinocytes from each other).

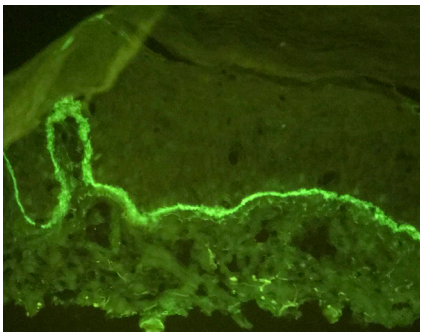
Bullous Pemphigoid = *"Pemphigoid"*

Pemphigoid is an autoimmune skin disorder caused by **IgG** antibodies directed against **hemidesmosomes** of the epidermal basal layer. The connection between the stem cells of the stratum basale and the basement membrane is lost. It is an antibody-mediated destruction of tissue, so is a type II hypersensitivity reaction. Only one cell type has a hemidesmosome—the basal cells attached to the basement membrane. Hemidesmosomes are not anywhere else in the entire epidermal layer. Every other cell is connected to its neighbor by desmosomes. In Pemphigoid, only the hemidesmosomes are affected. That means the entire epidermal layer **remains intact to itself** and that intact epidermal layer **lifts off the basement membrane** as **one intact unit**. The epidermis is continuous. There are some areas of skin that are not affected by the IgG separation, and those basal cells remain attached to the basement membrane. The areas that are affected lift off the basement membrane. But the squamous cells of the affected area are still attached to each other by desmosomes and attached to the cells of the unaffected areas by desmosomes, which in turn are attached to the basement membrane by unaffected hemidesmosomes of the basal cells attached to them. That means these blisters are strong—the full thickness of the epidermis-unattached-to-BM is connected to the full thickness of the epidermis-attached-to-BM. This creates **tense blisters** that can be fluid-filled. Tense blisters means they are not friable, and so there is a **negative Nikolsky** sign. Because Pemphigoid is not as bad as Vulgaris, Pemphigoid **spares the oral mucosa**.

A confirmation of the diagnosis is made on biopsy. That biopsy can be delivered in two ways: immunofluorescence or light microscopy. On **immunofluorescence**, there will be **linear IgG deposits** where the hemidesmosomes are—at the **dermal-epidermal junction**. This can also be described as a linear pattern over the basement membrane. On **light microscopy** we see a **subepidermal blister**—the dermis is the base of the blister, and the roof of the blister is an intact epidermis, including the stratum basale. It also happens (and we don't have a good way to remember why this happens) that the blister should be fluid-filled and be **eosinophil rich**.



(a)



(b)

Figure 3.3: Pemphigoid
(a) The auto-antibodies against hemidesmosome/basement membrane proteins in bullous pemphigoid cause the basal layer keratinocytes to detach from the underlying basement membrane. This creates a subepidermal blister where the entire epidermis is detached from the dermis leaving no keratinocytes remaining on the blister floor. Note the numerous eosinophils in the blister cavity, a common feature of bullous pemphigoid. (b) Direct immunofluorescence in bullous pemphigoid shows linear deposition of IgG (and complement C3) along the basement membrane just beneath the basal layer of the epidermis (corresponding to where the subepidermal blister forms).

Dermatitis Herpetiformis

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease. **Celiac disease** is an **autoimmune reaction** to gluten with the formation of **IgA antibodies**. These IgA antibodies (anti-endomysium, anti-gliadin, anti- transglutaminase) cause destruction of the intestinal villi and result in a malabsorption syndrome. Completely unrelated to that process in the gut, the same IgA against gluten deposits in the skin. Dermatitis herpetiformis is caused by **IgA depositions in the dermal papillae**, without any inflammatory reaction or destruction of the skin. It isn't even a hypersensitivity reaction—while there are deposits of IgA-antigen complexes, there isn't any immune destruction of the skin where they deposit.

This disease derives its name from the lesions that erupt. The lesions are herpes-like. They appear mostly as **intensely pruritic** papules, but often as tiny **vesicles** and sometimes bullae. Small vesicular lesions that are itchy or painful sounds a bit like the herpes virus. But these lesions can be anywhere on the body, not in common locations to contract herpes, and not in a dermatomal distribution for shingles. They are commonly found on the **extensors—elbows**, forearms, buttocks, and knees. If there is a "herpes-like rash" and it involves the elbows or buttocks, think dermatitis herpetiformis (careful buttocks: that could be a vasculitis, Henoch-Schönlein purpura).

If a history of celiac disease is given, a biopsy can be skipped. If a biopsy is performed, there will be an **immunofluorescence** pattern of deposition of IgA at the **tips of the dermal papillae**. The bright green will be in the dermis, and particularly concentration in the papillae.

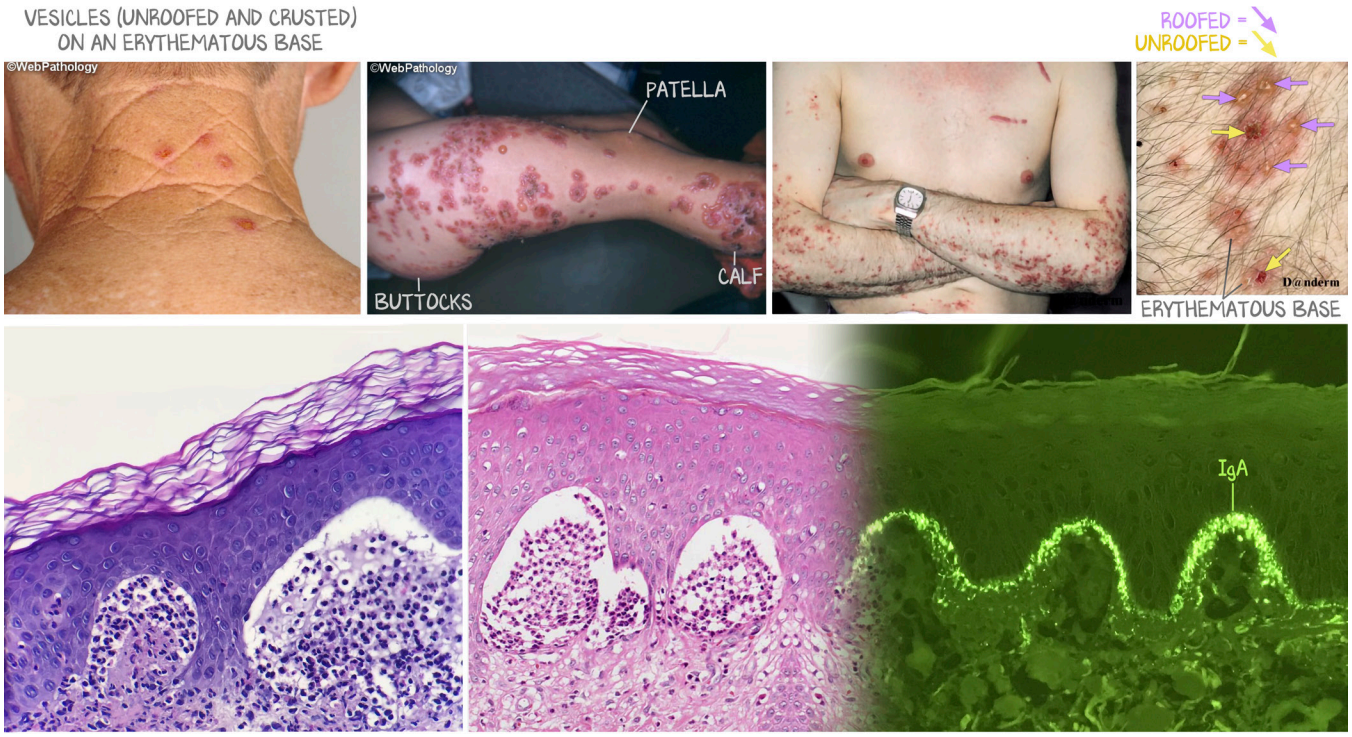


Figure 3.4: Dermatitis Herpetiformis
Dermatitis herpetiformis lesions are characterized by fine vesicles on an erythematous base—the same as herpetic lesions. However, dermatitis herpetiformis tends to occur on the extensors. As the image in the top left demonstrates, it need not be extensors alone, and as the image on the top right demonstrates, sometimes there is no erythema. It is crucial to identify this disorder's association with celiac disease and the immunofluorescent pattern—the dermal papillae are lined with immunofluorescence (IgA) but have an intact epithelium.

Treatment is with dapsone and a gluten-free diet. This is a board favorite because it starts as a rash with an immunofluorescent biopsy, but then flips to a question about gastrointestinal disease. In life, this might be how you get a patient with celiac diagnosed properly.

DISEASE	CHARACTERIZATION
Pemphigus vulgaris	**IgG** antibodies against **desmosomes** that hold all epidermal cells together (type 2 HSR) **Flaccid blisters** that **tear easily** (positive Nikolsky) and **are present** in the mouth IgG and C3 deposition surrounding all epidermal cells = **net-like immunofluorescence** Intra-epidermal blister with **tombstoning** at the basement membrane
Bullous pemphigoid	**IgG** antibodies against **hemidesmosomes** that hold the basal layer to basement membrane (type 2 HSR) **Tense, turgid blisters** that do not tear easily (negative Nikolsky) and do **not** present in mouth IgG deposition along the basement membrane = **linear immunofluorescence** Subepidermal blister with **intact epidermis** separated from BM, **eosinophil-rich** fluid
Dermatitis herpetiformis	**IgA** immune complex deposition at the **tips of dermal papillae**, inducing an elevation of epidermis Vesicular eruptions are intensely pruritic, look like herpes Manifests as **celiac disease** and as reaction to **gluten/gliadin** found in wheat products IgA antibodies are made to gliadin, endomysium, and transglutaminase

Table 3.2: Antibody-Mediated Bullous Diseases
The characterizations of each disease. This table is very purposefully not meant to compare diseases against each other.

Erythema Multiforme (EM)

EM is an **immune-mediated** disease that presents with cutaneous and mucosal lesions. Its pathogenesis has not been clearly defined, but it is believed to be a **cell-mediated** (type 4 HSR) immune response against viral antigens. The cell-mediated part is a near certainty. The viral antigen part is less certain. This is because EM eruptions can occur in correlation with far more than just viral infections. This is a sort-of-blistering disease that **can appear on the palms, soles, and the mouth, as well as skin**.

EM is a nonspecific finding associated with infections, drug reactions, cancers, and other autoimmune diseases. The **most common infection is HSV**, and the drugs that cause EM are the same ones you should associate with all cutaneous manifestations of drug reactions—**sulfa drugs**, **β-lactams,** and **phenytoin**. The cutaneous lesions themselves vary a lot (the disease is named "multi-form-e") and include non-target-like papules or vesicles and target-like lesions. Googling this rash will result with a variety of images, none of which looks like the others. Classically, and what you should learn, EM presents with **targetoid lesions.** The center of the lesion is usually dusky in color, or blistered. The surrounding ring is either erythematous or raised. The final ring is pink, more flesh colored but not back to normal. The mucosal lesions are harder to identify as EM, and appear to be more of an ulcer than a ring. If there is a **target lesion on palms or soles**, think EM or syphilis.

The minor form of EM does not involve the mucosa. The major form of EM does involve the mucosa. This distinction has very little utility, but is emphasized by some texts.

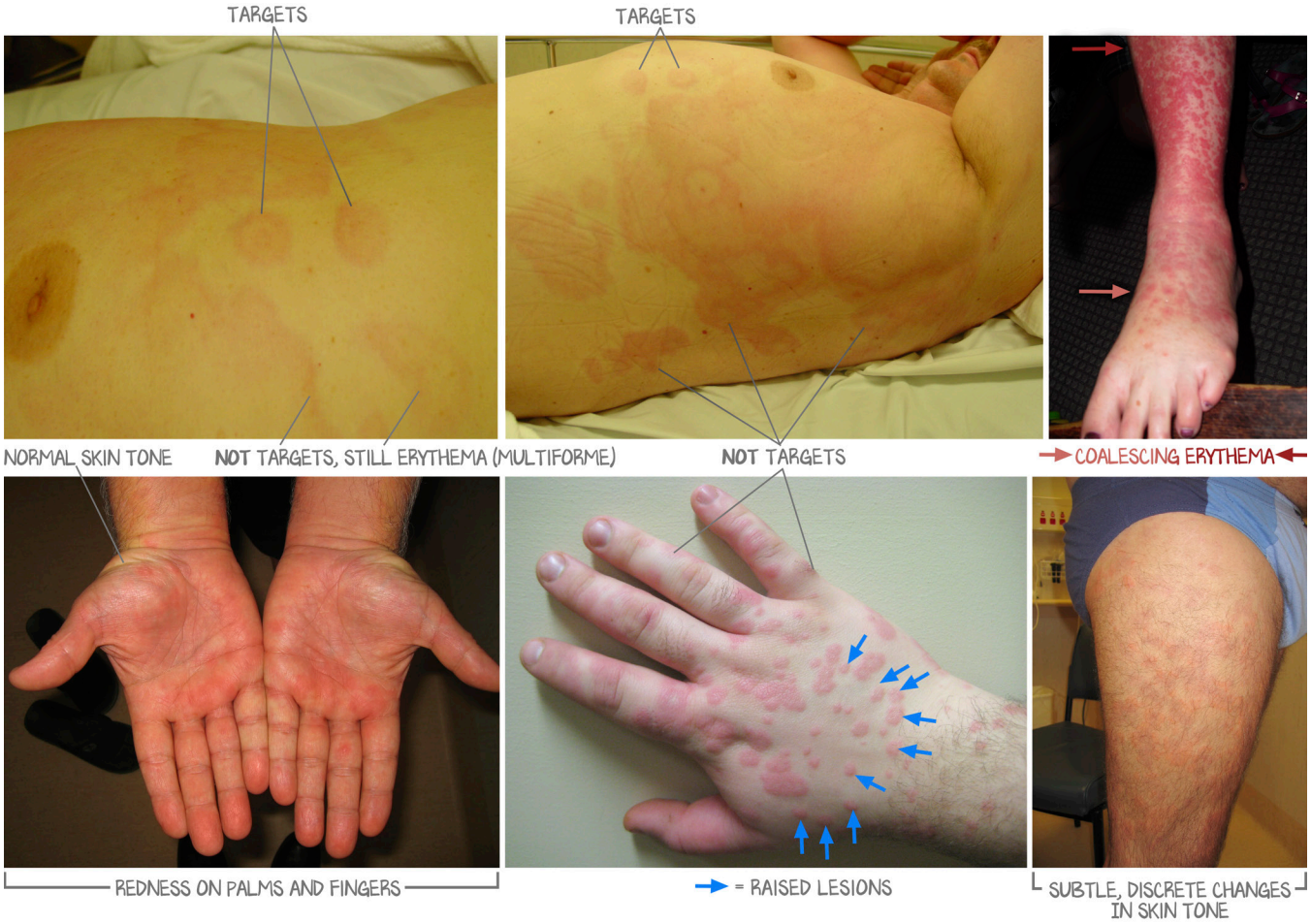


Figure 3.5: Erythema Multiforme
Classically depicted as a targetoid lesion found on the palms and soles, erythema multiforme is appropriately named—multiforme. Even in our one example with targetoid lesions, the same patient has violaceous aggregates of a rash outside the targets. Most cases aren't targetoid, and the rash can be inconsistent from person to person. This makes learning the subject very difficult, especially if you don't go into dermatology. But you should watch out for a red (erythematous) rash that develops after initiating a drug that can cause a fixed drug eruption.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN represent a continuation of the spectrum of disease with the pathogenesis of erythema multiforme. The disease is named by how much of the body's surface area is affected. The pathogenesis remains a **cell-mediated autoimmune** reaction (type 4 HSR) that leads to a severe **mucocutaneous necrotic reaction.** Erythema multiforme is localized to skin, SJS is more surface area covered with fever and mucosal involvement, and TEN is > 30% of the surface area being involved. In all conditions, there is **necrosis of skin**.

SJS/TEN happens in **young patients** (meaning all ages, not concentrated among the elderly like the antibody-mediated skin diseases), and almost always in response to an **offending agent**. Medications leading to SJS/TEN can be anything, but those commonly associated are **allopurinol, lamotrigine**, other **antiepileptics** (especially carbamazepine and phenytoin), **sulfonamide antibiotics** such as TMP/SMX (though β-lactams have been implicated), and anti-inflammatories like NSAIDs. Identification of the name of medication on a med list is not as helpful as finding an **addition of a new medication** in close proximity to the onset of the rash (days to weeks). The causative agent is likely to be the new medication. This is a rare but feared complication of hospitalization, where new intravenous medications are often introduced to the patient.

BODY SURFACE AREA INVOLVED	DIAGNOSIS
< 10% BSA	Stevens-Johnson Syndrome
10–30%	SJS/TEN overlap
> 30%	Toxic Epidermal Necrolysis

Table 3.3: SJS vs. TEN
The diagnosis is based on biopsy and how much of the body surface area is involved.

SJS/TEN starts with a systemic inflammatory reaction that activates the immune system. That initial systemic inflammation results in an acute, **influenza-like prodrome** with fever, malaise, and myalgias. After a few days, the fever breaks and is followed by **ill-defined erythematous macules** with **atypical target lesions**. In addition to the targets, there are erythematous macules that develop anywhere on the body. Then these erythematous macules (red splotches) begin to **coalesce**. The coalescing is followed by the **eruption of thin-walled bullae** which **slough off**, revealing ulcers.

PRODROME	INFLUENZA-LIKE REACTION, FEVER, MYALGIAS
Early SJS/TEN	Target-shaped lesions, erythematous macules
Middle SJS/TEN	Thin-walled, friable bullae
Late SJS/TEN	Sloughing of skin

Table 3.4: Progression of SJS/TEN
The diagnosis is unclear until the bullae erupt and skin begins falling off.

If biopsied, the lesion shows **necrosis** (necrosis, dead tissue, not antibody deposition) at the **dermal-epidermal junction**. When Pemphigoid was at the dermal-epidermal junction, the bullae were thick and didn't slough off. That was because there was no necrosis. When Vulgaris had friable thin blisters, it was because of desmosome destruction. In SJS/TEN, friable blisters occur because of epidermal necrosis, at the dermal-epidermal junction, and not the destruction of one of the structures that hold cells together.

DISEASE	CHARACTERIZATION
Erythema multiforme	Cell-mediated (type 4 HSR) reaction to viruses, medications, or cancer Causative agents are HSV, mycoplasma, sulfa drugs, phenytoin, β-lactams Target lesions that can involve the palms and soles
SJS/TEN	Cell-mediated (type 4 HRSHSR) reaction to a medication Causative agents are sulfa drugs, β-lactams, lamotrigine, allopurinol, anti-epileptics Flu-like prodrome, erythematous macules, friable blisters, sloughing of skin Biopsy shows necrosis at the dermal-epidermal junction

Table 3.5: Cell-Mediated Bullous Diseases
The characterizations of each disease. This table is very purposefully not meant to compare diseases against each other.

Citations

Figure 3.1b: Originating from the University of Alabama at Birmingham, Department of Pathology PEIR Digital Library at http://peir.net pursuant to a license grant by the UAB Research Foundation.

Figures 3.2a, 3.2b, 3.3a, 3.3b, 3.4: Courtesy of Jerad M. Gardner, MD.